



Review Article

Hyperthermia and Breast cancer: A short review

Bora Uysal*

Gulhane Education and Research Hospital, Radiation Oncology Department, Etlik Kecioren Ankara, Turkey

***Address for Correspondence:** Bora Uysal, Gulhane Education and Research Hospital, Radiation Oncology Department, Etlik Kecioren Ankara, Turkey, Tel: 0 312 304 46 89, Email: drborauysal@windowslive.com

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Abstract

The main goal of hyperthermia is to elevate the tumor temperature to kill tumor cells and improve local control. The usage of hyperthermia is combination with radiotherapy or chemotherapy. Hyperthermia is delivered in different types of cancers like breast cancer, melanoma and sarcoma. Breast cancer treatment enroll surgery, chemotherapy, radiotherapy and hormone therapy. Hyperthermia is given once or twice a week concomitantly with radiotherapy or chemotherapy. This short review will enlighten the types, physics, and the results of hyperthermia especially in the management of breast cancer therapy.

Introduction

Hyperthermia (HT) is a radiosensitizer and also a cytotoxic treatment modality. HT inhibits lethal damage and sublethal damage repair. Different devices are used but no gold standart equipment is advised by authorities. HT kills tumor cells itself or sensitize them for the treatment outcomes for chemotherapy and radiotherapy. Thermotolerance is a special condition that immune response occurs against tumor cells after usage of HT.

Combination of hyperthermia and chemotherapy

Cisplatin, cyclophosphamide, bleomycin and mitomycin C have synergistic effects with HT. Firstly HT inhibits repair and increase DNA damage, cellular uptake of medicines and free radicals. It also helps to prevent from drug resistance. Optimal timing of HT and chemotherapy usage is not known but 5-FU and HT can be given simultaneously or be given before HT. Current data is not all but some drugs have synergistic interaction with HT. Trimodality treatment enrolls HT, radiotherapy and chemotherapy (Table 1).

Concomitant usage of radiotherapy and hyperthermia

G2 and M phase of cell cycle is radiosensitive and S phase is radioresistant. The cells in S phase start to be radiosensitive after HT. Reoxygenation with HT leads good response with radiotherapy (RT) because hypoxic cells are so radioresistant. HT blocks

Table 1: Studies of combination of hyperthermia with radiotherapy, chemotherapy and immunotherapy.

Immunotherapy and hyperthermia	Chemotherapy and hyperthermia	Radiotherapy and hyperthermia
Takeda (2013)	Zhuou (2015)	Oldenborg (2015)
	Yamamoto (2015)	Linthorst (2015, 2016)
		Refaat (2015)
		Van der Zee (1999, 2010)
		Varma (2012)
		Iemwananonthachai (2003)
		Moros (2010)



lethal and sublethal damage pathways TER (thermal enhancement ratio) is a ratio of the needed doses with just radiotherapy and combined RT and HT to get an isoeffect. Although HT and RT improve local control when combined, the complications as bone necrosis, fibrosis or fistula should be known (Table 2).

Physics

The definition of HT is to elevate tumor temperature between 40 and 45 centigrad degree for one hour. The final effect doesnt occur same in very tissue because of the location containing fat, water or bone.

HT can be delivered via three modalities. Ultrasound, thermal conduction and nonionizing electromagnetic radiation are the major devices used for HT.

Ultrasound

Simply, the transfer of energy from acoustic field device to selected location is ultrasound heating. Superficial tissue is heated with ultrasound but some anatomic areas in body don't let the physicians to achieve better results. This problem limits the use of ultrasound. Superficial and deep heating devices can be used but care should be taken not to cause a complication of the bone or the other tissues especially in deep heating.

Thermal conduction

Thermal conduction is delivered with needle, surface pad or catheter that hot water circulating in. 0.5-30 mhz radiofrequency electrodes are used for interstitial heating. This method is highly selective, sensitive and also give inhomogeneous dose to the tissue like brachytherapy. The popularity of thermal conduction is limited because of a decreasing usage of brachytherapy devices.

Clinical hyperthermia

Supraphysiologic elevation of temperature to the 40-45 centigrad degree in 1 hour is mostly known definition of HT. Firstly, HT had been used for metastatic tumors There are several trials enrolling HT and chemoradiotherapy or radiotherapy combinations. Esophagus, bladder and sarcomas are the locations of usage of chemoradiotherapy and HT combination and head and neck, melanoma, breast, brain, cervix, rectal, bladder and nasopharynx cancer are the locations of usage of radiotherapy and HT combination [1].

HT in the treatment of breast cancer

It is known that breast cancer is the most frequent malignancy among women. Chemotherapy and also radiotherapy are used in the management of breast cancer according to the stage and other factors.

Discussion

Hyperthermia-integrated chemotherapy is a new milestone for effective treatment [2]. The local recurrence years after locoregional and systemic therapy of breast cancer is a challenging issue to be discussed. In a article by Oldenberg et al., 8x4 Gy or 12x3 Gy was delivered combined with HT once or twice a week. HT and reirradiation resulted with effective and outstanding palliative in these group [3].

Table 2: Types of Hyperthermia.

Microwave
Radiofrequency
Ultrasound waves
Infrared
Laser
Magnetic induction

HT and RT modalities were used in unresectable local recurrences and concomitant usage improved local control rates with slight side effects. The dose delivered for RT was 32 Gy in 4 fractions and HT was given once a week in this period [4]. Animal studies have been done for the evaluation of different T modalities by Petryk et al. Magnetic nanoparticle and microwave hyperthermia were compared and nanoparticle treatment resulted in slightly better effective and reduced normal tissue damage than microwave HT [5].

36 reconstructed breast cancer patients treated with reirradiation and HT were examined for the toxicities and grade 2 and 3 toxicity were seen in 7 patients and just one needed reoperation. This data showed that RT and HT can be an effective and safe option in reconstructed breast cancer patients [6]. HT and chemotherapy combination was used for the management of advanced recurrent breast cancer study group and it was tolerable and efficient according to the results of Yamamoto et al, [7]. Refaat et al. studied HT and RT for 127 locally advanced or recurrent breast cancer patients. HT was delivered twice a week after RT. The effectiveness was shown and local control and also overall survival were improved compared to historical results with only RT [8]. The efficiency of HT in the management of unresectable skin metastases was shown in a 66-year-old female. HT actually have a supraadditive effect on RT and chemotherapy in this case. The tumor became nearly flat after HT [9].

Combination of HT and RT appear to have higher complete response rates compared to only RT modality. Totally 32 Gy of 8 fractions was delivered and 4 or 8 HT sequences were given concomitantly. Superficial hyperthermia was used with 433 MHz [10]. In an article by Takeda et al., recurrent or advanced stage breast cancer patients were treated with immunotherapy, HT or combination of both. 23 of 712 patients have better outcomes with combination [11]. The usage of HT and RT improves local control. Randomised comparison of chest wall HT in heated and nonheated sectors was studied by Varma et al. Locally advanced breast cancer patients enrolled in this study. Same dose was given for all. No difference in late toxicity was shown after all between these groups [12].

HT gives better palliative results if combined with RT for recurrent breast cancer patients. This is associated with local control and radiosensitization of tumor by HT. Local control rate was 73% in this last study by Van der Zee [13]. The timing of HT differs in neoadjuvant, definitive and adjuvant treatment of breast cancer [14]. Ulcerative advanced breast cancer patients are a challenging issue because of the management. 12 of cases were treated with HT in 43 centigrad degrees and 20-70 Gy RT. Palliation and slightly local control were resulted after combination of therapies [15]. Usage of HT depends on clinical basis. In a study by Ben-Yosef et al, 2 patients were treated with HT adjuvantly. One of them has a positive deep surgical margin and the other has second local recurrence in chest wall [16]. IMRT and HT combination started to be used in some centers and it is encouraging to see these modalities to enlight the future studies [17].

Conclusion

In this short review, HT was discussed with current literature. It is crystal-clear that not all but some oncology institutions have HT devices. HT is needed to have experts as oncologists and also technicians. Breast cancer treatment is vital because of frequency and the treatability of this type of cancer. Local control is improved with combinations of HT, RT and chemotherapy and there is a tendency to get better results for survival curves in the future.

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